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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,561	08/25/2003	Michael David Bentley	034848/268660	3230

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NEKTAR THERAPEUTICS
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EXAMINER	
HEARD, THOMAS SWEENEY	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
07/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/647,561	BENTLEY ET AL.	
	Examiner	Art Unit	
	THOMAS S. HEARD	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-16,18,19,23,24,26 and 27* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-16,18,19,23,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief filed on 3/9/2009, PROSECUTION IS HEREBY REOPENED. New Grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing this action.

Claim(s) 1-3, 6-16, 18, 19, 23, 24, 26, and 27 are pending. Claim(s) 24 are withdrawn. Claims 1-3, 6-16, 18, 19, 23, 26, and 27 are hereby examined on the merits.

Response to Arguments

Applicant's arguments over the 35 USC § 103 with respect to Claims 1-3, 6-16, 18, 19, 23, 26, and 27 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. V. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976);In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

Claims 1-3, 6-19, 23, 26 and 27 rejected under 35 U.S.C. 103(a) as being unpatentable over

Abbruscato TJ, et al, "Blood-to-central nervous system entry and stability of biphalin, a unique double-enkephalin analog, and its halogenated derivatives," J Pharmacol Exp Ther. 1996 Mar;276(3):1049-57 and

Delgado C, Francis GE, Fisher D., "The uses and properties of PEG-linked proteins," Crit Rev Ther Drug Carrier Syst. 1992;9(3-4):249-304 (made of record in the previous office action), **or**

Ekwuribe et al, WO 01/19406.

The instantly claimed invention is drawn to a hydrophilic polymer-peptide conjugate consisting of a peptide that is either biphalin (Applicant's elected species) or [D-Pen2, D-Pens] enkephalin (DPDPE) covalently linked to one or more water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons and selected from either poly(ethylene glycol) or copolymers of ethylene glycol and propylene glycol, wherein said conjugate, when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier

Abbruscato TJ, et al teaches the blood to CNS entry and stability of biphalin. Abbruscato teaches that after systemic administration only a small amount of biphalin was detected in the brain, but analgesia was detected, teaching that biphalin is capable of entering the CNS. Abbruscato et al teaches that improved CNS entry of a biphalin analog, that of a chlorohalogenated biphalin was achieved due to enhanced lipophilicity and through enhanced stability., see abstract, and page 1050, column 1 and third paragraph. Abbruscato et al teaches that this study which incorporated chlorohalogens into biphalin is a promising structural modification in the development of biphalin as a successful opoid drug to the clinic, see abstract. Abbruscato et al does not teach the pegylation of biphalin for improved stability or improved CNS uptake.

Delgado et al teaches the beneficial uses and properties of PEG-linked proteins and peptides. Delgado et al et al teaches that the addition of the Peg adds both hydrophobic (lipophilic) and hydrophilic properties to the PEG conjugated peptide. Delgado et al teaches a wide range of benefits of PEGylating a protein which are 1) increased plasma half-life, 2) reduced renal clearance, 3) reduced cellular clearance, 4) reduced proteolysis, 5) reduced immunoclearance, 6) reduced immunogenicity and antigenicity, and 7) increased solubility, among 8) other properties of the PEG-protein conjugates. Unrelated PEG-proteins are shown to have these beneficial properties demonstrating the broad acceptance of the conjugated PEG to the proteins, and that the PEG is determining the property. Delgado et al further teaches mono-pegylation, bi- and multiple-pegylation, N-terminal PEGylation and PEGylation in ranges from 700 to 70,000 MW readable upon PEG ranging from 10 to 2000, readable on Claims 3, 6-10, 11-16, 18-19, 26, and 27. Note that in Claim 3 is a negative limitation that is readily apparent in the examples of Delgado et al, see Figure 3 for example. The linkage to the Tyrosine as claimed in Claim 19 would be at the N-terminus because the Tyrosine is the N-terminal amino acid and meets the limitation of those Claims 19 as well as Claim 6 and 7. Delgado et al teaches a plurality of different PEG moieties readable upon co-polymers of Claim 8 as well as polyethylene glycol of Claims 1, 6, 7, 10-, 18, 19, 26, and 27.

Ekwuribe et al teaches the conjugating of PEG to a drug to make a prodrug that is capable of crossing the blood brain barrier (BBB). On page 11 of the WO document, for a PEG conjugated drug molecule, PEG can both increase lipophilic or hydrophilic

properties of the attached drug. The PEG also functions to enhance the delivery of compounds that can enter the CNS via the BBB, or deliver compounds that cannot otherwise be delivered through the BBB into the CNS. Ekwuribe et al, therefore, adds yet another beneficial property of PEG to the attached drug, to those already related in the Delgado et al reference supra.

It would have been obvious to one of ordinary skill in the art to PEGylate neuropeptide biphalin as taught by Delgado et al, in substitution for the chlorohalogenation taught by Abbruscato et al for the common purpose of increased stability of the peptide. One would have been motivated to do so given that Delgado et al teaches improved pharmacokinetic profiles for peptides and proteins that are PEGylated. The improved pharmacokinetics of PEGylated proteins taught by Delgado come from increased plasma half-life, reduced renal clearance, reduced cellular clearance, and reduced proteolysis. Because one would expect greater stability of the PEGylated biphalin peptide, one would also expect an improvement of the PEGylate biphalin to cross the BBB given that stability was one of the contributing factors in the increased CNS uptake of biphalin as taught by Abbruscato et al, and pegylation of proteins and peptides provides this property. One would have had a reasonable expectation of success in Delgado et al teaches that PEGylating peptides is routine, that such PEGylation provides improved performance in at least eight (8) areas important in pharmacology, and that these improved properties are not protein dependent. Additionally, one would have been motivated to PEGylate the biphalin because Ekwuribe et al teaches that pegylating drugs add an additional property of allowing the

drug to be transported across the BBB. Note that Claims 1 and 2 are claims to results that are the effective outcome of PEGylating a protein and would necessarily follow upon pegylation of biphalin, that of the ability to cross the BBB.

From the teachings of the references supra, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention, that of pegylating a neuropeptide. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, and the invention as claimed, is rejected under 35 U.S.C. 103(a).

Applicant's Arguments

Applicant's arguments will be address to the extent it reads on the new rejection set forth supra, and the only argument to address is that of Delgado et al. Applicants have argued that Delgado et al does not teach nor suggest a biphalin peptide-peg conjugate, let alone that the biphalin-peg conjugate would cross the BBB.

Response to Applicants Arguments

Applicants arguments have been carefully considered but are not deemed persuasive to overcome the rejection. Delgado et al does not need to teach or suggest the pegylation of biphalin and does not need to. The pegylation art is a very well known art and peptide/protein modification. This very common modification was shown to provide common properties that were peptide independent, making the PEG the moiety that conferred the beneficial and desired property. The fact that it does not teach that

PEGylating proteins allows them to cross the BBB, or that it did not teach biphalin as one of the proteins to be pegylated is completely irrelevant. Delgado et al teaches and provides multiple reasons with beneficial properties to modify a protein or a peptide, and silence on biphalin, or that PEGylation of biphalin allows the peptide to cross the BBB, is of no consequence to the patentably of a PEG-biphalin conjugate. Though the incxreased stability if bibpalin, once conjugated to PEG as taught by Delgado et al, does increase stability and this property increase is directly related to the uptake of a peptide that already crosses into the CNS as taught by Abbruscato et al. The reasons to PEGylate a protein or peptide are numerous and the motivation to do so does not have to fall within the motivation or reasons the Applicants want to PEGylate their protein of choice. The invention is drawn to a known protein, biphalin, and is modified by a well knows technique, which is corroborated by Applicants submission of Shearwaters Catalog for pegylation of proteins and peptides. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, and the invention as claimed, is rejected under 35 U.S.C. 103(a).

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Prior art contained in the reference of record can be applied in the next office action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas S. Heard whose telephone number is (571) 272-2064. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thomas S Heard/
Examiner, Art Unit 1654

/Cecilia Tsang/

Supervisory Patent Examiner, Art Unit 1654